REMARKS/ARGUMENTS

In response to the Office Action of December 7, 2004, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Claim Status/Support for Amendments

Claim 1 has been amended. Claims 2-38 have been cancelled. Claims 39-46 have been added.

Claim 1 is currently under examination. Claims 1 and 39-46 remain pending in the instant application.

No new matter has been added by the amendments to the specification made herein.

The title has been amended at the suggestion of the Examiner to more clearly indicate the invention to which the pending claims are drawn.

In the "Background of the Invention" section a punctuation error was corrected at page 1, line 23.

The description of the reference at page 5 has been amended to correct a typographical error in the international application number. The corresponding international publication number has also been added.

The "Description of the Figures" section has been amended to add sequence identification numbers and to clearly indicate that

Figures 2 and 3 show the mass spectrum profiles of the disclosed biopolymer markers (SEQ ID NOS:1 and 2).

Several protocols at pages 40-45 have been amended to properly identify trademark names (SEPHAROSE, TRITON, TRIS and EPPENDORF). The protocol titles at page 41 (lines 6 and 20), page 42 (line 12) and page 43 (lines 3 and 16) were underlined in the original disclosure and do not indicate text which was amended herein.

In the "Detailed Description" section, the term "cerebrospinal fluid" has been added to define the abbreviation "CSF" at page 49, line 8 in order to provide explicit support for cerebrospinal fluid as recited in claim 41. "CSF" is a well known abbreviation for cerebrospinal fluid in the biochemical art. A typographical error within the same paragraph has also been amended (skill replaced skilled).

The abstract has been amended to remove the legal phraseology ("said").

No new matter has been added by the amendments to the claims made herein.

Claim 1 has been amended to explicitly claim the biopolymer markers (SEQ ID NOS:1 and 2). The term "biopolymer marker" is used throughout the specification as originally filed, see, for example, page 1, line 8.

No new matter has been added by the addition of claims 39-46. Claim 39 clearly discloses the relationship between the presence

of the claimed biopolymer markers (SEQ ID NOS:1 and 2) and Type II diabetes and explicitly indicates how the presence of the claimed biopolymer markers is determined from mass spectrum profiles (see the specification, as originally filed at, page 35, lines 14-18, page 46, lines 4-10 and Figures 1-3). The subject matter of new claims 39-46 corresponds with subject matter originally found in cancelled claims 2-38. The above additions to the claims also find basis in the original disclosure at page 25, line 16 to page 26, line 22. The method of new claim 39 is described in detail at pages 37-47. Page 47, lines 19-23 refers to use of various types of samples and page 38, line 20 to page 39, line 10 refer to different mass spectrometric techniques. Page 46, line 19 refers to practicing the claimed methods with a human patient. Page 36, lines 9-12 and pages 47-48 describe kits contemplated for use with the claimed methods. Page 47, lines 14-19 refers particularly to the immobilizing on solid supports and labeling of components of the contemplated kits. It is clear from these specific recitations and from the description of methods utilized that the methods and types of kits recited in the newly added claims (39-46) were fully contemplated by the inventors at the time of filing and were enabled by virtue of the disclosure as originally filed.

Restriction

Applicants herein affirm the election of Group I (claims 1 and 2), with traverse, for prosecution on the merits. The election was made by Ferris Lander during a telephone conference with the Examiner on August 6, 2004.

Information Disclosure Statement

The Examiner has pointed out that the listing of references in the specification is not a proper Information Disclosure Statement. 37 CFR 1.98(b) requires a list of all patents, publications or other information submitted for consideration by the Office, and MPEP 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Thus, the Examiner indicates that unless the Examiner on PTO-892 form or Applicant on PTO-1449 form has cited the references they have not been considered.

The Examiner indicates that the Information Disclosure Statements filed on April 2, 2002 and March 25, 2003 have been considered as to the merits prior to the first action.

The references cited within the specification but not included in the above-mentioned Information Disclosure Statements provide general information relating to background information and/or the state of the art, but were not deemed pertinent to the patentability of the claimed invention.

Objections to the Specification

The Examiner notes that the specification has not been checked to the extent necessary to determine the presence of all possible minor errors.

The Examiner alleges that the title of the invention is not descriptive and has required a new title that is clearly indicative of the invention to which the claims are directed.

The title has been amended to comply with the Examiner's suggestion.

The Examiner points out a typographical error at page 1, line 23, in which parentheses were not closed in the text. The instant specification has been amended to correct this and other similar kinds of errors.

The Examiner notes the use of trademarks in the application (i.e. SEPHAROSE on page 40, line 23 and TRITON on page 42, line 8) which should be capitalized wherever they appear and be accompanied by the generic terminology. The Examiner further notes that although the use of trademarks is permissible in patent applications; the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Applicants have amended the specification at pages 40-45 to properly identify trademark names (SEPHAROSE, TRITON, TRIS and EPPENDORF).

The Examiner points out guidelines for the proper language and format of an abstract of a patent application and objects to the abstract of the instant application as it recites the legal phraseology "said".

The abstract of the instant application has been amended herein to remove the legal phraseology "said".

Applicants have now addressed all of the Examiner's objections and respectfully request that the objections to the specification be withdrawn.

Rejection under 35 USC 101

Claims 1 and 2, as amended on April 2, 2002, stand rejected under 35 USC 101 because the claimed invention is allegedly directed to non-statutory subject matter.

The Examiner alleges that the invention as claimed reads on any biopolymer marker consisting of SEQ ID NO:1, SEQ ID NO:2 or an analyte thereof wherein the analyte thereof would read on products of nature absent the isolation of said analyte thereof.

The Examiner recommends amending the claims to incorporate the language "isolated" or "purified" to overcome the rejection.

Claim 1 has been amended herein to specifically recite isolated biopolymer markers (SEQ ID NOS:1 and 2) and claim 2 has been cancelled. As used within the instant specification(at page 20, lines 9-16), the term "isolated" is interpreted to mean

"altered by the hand of man" from its natural state, for example, if it occurs in nature and it is then "isolated", it has been changed or removed from its original environment or both. Polypeptide markers, such as those claimed herein (SEQ ID NOS:1 and 2) naturally present in a living organism are not "isolated", however the same polypeptide markers separated from the co-existing materials of their natural state are "isolated". It is clear from the methods recited herein that the claimed polypeptide markers (SEQ ID NOS:1 and 2) are obtained from samples which have been isolated from a patient's body, thus the claimed polypeptide markers are "isolated" (see page 31, lines 13-14 and page 31, line 23 to page 24, line 7, for example).

Accordingly, it is respectfully submitted that Applicants have now shown that the claimed invention is drawn to patentable subject matter. Thus, Applicants respectfully request that the above rejection under 35 USC 101 be withdrawn.

Rejections under 35 USC 112, second paragraph

Claims 1 and 2, as amended on April 2, 2002, stand rejected under 35 USC 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

Applicants respectfully disagree with all of the Examiner's assertions.

The Examiner alleges that claim 1 is indefinite for being in improper Markush format.

Claim 1 has been amended to recite "...selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:2". Thus, claim 1, as presented herein, is in proper Markush format.

The Examiner alleges that the term "having" in claim 1 is indefinite because it is not clear as to what the sequence will encompass. Specifically, it is not clear whether "having" is considered open (comprising) or closed (consisting of) language.

Claim 1 has been amended to remove the term "having" and now recites the closed language, "consisting of". The term "having" is not recited in any of the remaining pending claims.

The Examiner alleges that claims 1 and 2 are indefinite because it is unclear as to what the phrase "at least one analyte thereof" is intended to define.

Claim 1 has been amended to remove the phrase "at least one analyte thereof" and claim 2 has been cancelled. The phrase "at least one analyte thereof" is not recited in any of the remaining pending claims.

The Examiner alleges that claims 1 and 2 are vague and indefinite because the biopolymer is "indicative" of at least one particular disease state in claim 1 and "predictive of" Alzheimer's disease in claim 2. The Examiner alleges that "indication" and "predictability" are relative terms, which render the claims

indefinite. The Examiner further alleges that it is not clear as to how the measurement of the biopolymer markers will further serve to indicate a particular disease or predict Alzheimer's disease. It is not clear as to how the marker will identify Alzheimer's disease because a correlation of the markers with Alzheimer's disease is not disclosed in the specification.

Claim 1 has been amended to remove the term "indicating" and claim 2 has been cancelled. "Predictability" is not recited in any of the remaining pending claims. The recitation of "Alzheimer's disease" in claim 2, as originally filed, was an inadvertent typographical error; the instant application is drawn specifically to Type II diabetes (see Figure 1 and page 46, lines 4-10).

The claims have been amended to recite that the claimed biopolymer markers (SEQ ID NOS:1 and 2)are indicative of a link to Type II diabetes. According to the web site dictionary.com the term "linked" refers to the condition of being associated with or connected to (see attached document as accessed from the internet; reference 1). The instant specification fully supports a connection and/or association of the claimed biopolymer markers (SEQ ID NOS:1 and 2) with Type II diabetes. Page 35, lines 14-18 of the instant specification, as originally filed, states that an objective of the invention is to evaluate samples containing a plurality of biopolymers for the presence of disease specific marker sequences which evidence a link to at least one specific disease state.

The claims, as amended herein, do not recite that the claimed biopolymer markers are indicative and/or predictive of any disease state.

Accordingly, Applicants have now clarified the metes and bounds of the claims and respectfully request that the above-referenced rejections under 35 USC 112, second paragraph be withdrawn.

Rejection under 35 USC 112, first paragraph

Claims 1 and 2, as amended on April 2, 2002, stand rejected under 35 USC 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter, which allegedly was not described in the specification in such a way as to enable one skilled in the art to which it pertains or with which it is most nearly connected, to make and/or use the invention.

The Examiner makes the following assertions:

Claims 1 and 2 are directed to biopolymers consisting of SEQ ID NOS:1 and 2 indicative of Alzheimer's disease. The Examiner contends that the specification does not support this assertion. The specification (in particular page 46) and the figures do not definitively correlate the claimed markers consisting of SEQ ID NO:1 and SEQ ID NO:2 to Alzheimer's disease. The specification recites that the biopolymers consisting of SEQ ID NO:1 and SEQ ID No:2 were found in the serum of patients suffering from Alzheimer's

disease on page 46, but the specification does not contain any data supporting this contention and the figures do not identify SEQ ID No:1 and SEQ ID NO:2. Therefore, it is unclear how SEQ ID NO:1 and SEQ ID NO:2 were identified as "notable" or how they were deemed "evidentiary" of a disease state. There is nothing in the disclosure that would enable one to choose SEQ ID NO:1 or SEQ ID NO:2 as a notable sequence among an infinite number of possible proteins or peptides present in a patient sample.

Applicants respectfully disagree with all of the Examiner's assertions.

The recitation of "Alzheimer's disease" in claim 2, as originally filed, was an inadvertent typographical error; the instant application is drawn specifically to Type II diabetes (see Figure 1 and page 46, lines 4-10).

Applicants note that the isolated biopolymer markers (SEQ ID NOS:1 and 2) are linked to Type II diabetes.

According to the web site dictionary.com the term "linked" refers to the condition of being associated with or connected to (see attached document as accessed from the internet; reference 1). The instant specification fully supports a connection and/or an association of the claimed markers with Type II diabetes. The instant specification states at page 35, lines 14-18 that an objective of the invention is to evaluate samples containing a plurality of biopolymers for the presence of disease specific

biopolymer marker sequences which evidence a link to at least one specific disease state.

The "test of enablement" is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the prior art without undue experimentation (see MPEP 2164.01).

Furthermore, the decision in *In re Brandstadter* (179 USPQ 286; MPEP 2164.05) has established that the evidence provided by applicant (to overcome an enablement rejection) need not be conclusive but merely convincing to one of skill in the art.

Applicants respectfully submit that the instant specification provides sufficient evidence to convince one of skill in the art that the claimed markers (SEQ ID NOS:1 and 2) are linked and/or associated with Type II diabetes.

Claim 1 has been amended to specifically recite isolated markers selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:2, markers which the instant specification identifies as related to Type II diabetes (see page 46, lines 4-10). The phrase "consisting of" is closed language and excludes any element, step or ingredient not specified in the claims (see MPEP 2111.03). Thus, the scope of claim 1 is limited to these specific markers (SEQ ID NOS:1 and 2).

The descriptions of the figures have been amended to clarify that the data shown in the figures is representative of the claimed

peptides.

At page 46, lines 4-10 of the specification as originally filed, SEQ ID NO:1 is identified as having a molecular weight of about 1624 daltons. The description of Figure 2 at page 37 indicates that the spectra depicted in the figure is that of ion 1624. At page 46, ion 1624 is identified as an ABC transporter permease protein. The spectra shown in Figure 2 was obtained from Band 3-2 (resolved from a sample obtained from a control patient; normal with regard to Type II diabetes) as shown in the gel of Figure 1.

Likewise, at page 46, lines 4-10 of the specification as originally filed, SEQ ID NO:2 is identified as having a molecular weight of about 1552 daltons. The description of Figure 3 at page 37 indicates that the spectra depicted in the figure is that of ion 1552.

Figure 1 demonstrates that the biopolymer marker (Band 3-2; SEQ ID NO:1) is present in body fluid samples obtained from control patients (normal with regard to Type II diabetes), but is not present in body fluid samples obtained from patients having Type II diabetes. Thus, a difference is seen between two comparable samples, suggesting that the differentially expressed peptide is linked to Type II diabetes.

The specification, as originally filed, provides a precise protocol on how to analyze the data obtained from the disclosed

method. Page 25, line 16 to page 26, line 2 of the instant specification discloses a general outline of how to analyze the data obtained by carrying out the disclosed methods. Page 26, lines 6-13 of the instant specification further describes how samples were compared to develop data and indicates how biopolymer marker peptides were selected as notable sequences. This passage of the instant specification also discloses how certain peptides were selected from a plurality of molecules found within a sample and how peptides were deemed evidentiary of a disease state. Page 5, lines 12-20 also describes how biopolymer markers are evaluated according to the methods of the instant invention. Page 46, lines 18-20 of the instant specification clearly states the steps of the invention include obtaining a sample from a patient and conducting an MS analysis (mass spectrometry) on the sample. Mass spectrometry is commonly practiced and one of skill in the art would know how to analyze and obtain information from mass spectrometry profiles. It is clear that the data presented in the instant specification was obtained by carrying out mass spectrometry. Thus, Applicants assert that the specification, as originally filed, provides a precise protocol on how to analyze the data obtained by the disclosed protocol.

Additionally, Applicants respectfully submit that such protocols are common practice in the field of proteomics. For example, Lubec et al. (see attached abstract Journal of Neural

Transmission Supplement 57:161-177 1999; reference 2) disclose an experiment in which proteomic techniques, specifically electrophoresis and mass spectrometry, were carried out to detect differences in protein expression between Down's syndrome patients, Alzheimer's patients and "normal" control patients. In a manner similar to that of the instant inventors, Lubec et al. analyzed the increase and/or decrease in expression of a particular protein (DRP-2) when hypothesizing about the neuropathological findings in Alzheimer's disease and Down's syndrome.

Furthermore, Applicants assert that those of skill in the art are both highly knowledgeable and skilled and it is obvious that no undue experimentation would be required for a skilled artisan to follow any of the electrophoretic, chromatographic and mass spectrometric protocols presented in the instant specification in order to use the claimed invention. One of skill in the art would be able to view a gel, such as that shown in Figure 1 from which the claimed marker was identified (SEQ ID NO:1), and recognize a difference between two comparable samples (disease state vs. non-disease state) and further recognize that the peptides present within the gel are differentially expressed between the two sample types.

Figure 1 is a photograph of a gel showing the results of DEAE 1 resin (anion-exchanging) column chromatography as carried out with a set of 9 samples; 4 serum samples from "normal; with regard

to Type II diabetes" control patients (lanes 1-4, as read from the left), 4 serum samples from patients having Type II diabetes (lanes 5-8, as read from the left) and 1 samples of normal serum (pooled from a plurality "normal" patients; lane 9, as read from the left). Patient serum samples, shown in lanes 1-4 and 9, display a band, numbered Band 3-2, from which the claimed marker (SEQ ID NO:1) was isolated. These patients are all patients who were designated as "normal" with respect to Type II diabetes.

The data presented in the figures, derived from the working examples, discloses that the claimed marker (SEQ ID NO:1) is differentially expressed between Type II diabetes and a normal physiological state (with respect to Type II diabetes), thus it can be reasonably predicted that such a marker is linked to Type II diabetes. Furthermore, the figures identify SEQ ID NOS:1 and 2 and the specification discloses how such sequences were identified as notable in relation to Type II diabetes.

Thus, Applicants contend a skilled practitioner would find that the data presented in the instant specification is convincing with regard to a link between the claimed biopolymer markers (SEQ ID NOS:1 and 2) and Type II diabetes.

Considering the above comments, it is clear that both the specification and the prior art disclose how to make and use the instant invention. Accordingly, Applicants respectfully contend that the instant invention satisfies the "test for enablement"

since one skilled in the art could make or use the invention from the disclosures in the specification coupled with information known in the prior art without undue experimentation.

The Examiner makes a series of assertions regarding the enablement of subject matter which is not claimed, including the following:

The Examiner asserts that there is no correlation between the procedure for screening samples from patients suspected of having a variety of different diseases, the presence/absence of SEQ ID NOS:1 and 2; and the determination, prediction, assessment of at least one particular disease state like Alzheimer's disease. There is no disclosure enabling the use of the biopolymer marker with regard to regulating the presence or absence of said marker. The disclosure is lacking any teaching for how the identified sequence will be utilized to identify therapeutic avenues and regulation of a disease state. There is no disclosure designating how the sequence could be utilized therein, enabling one of ordinary skill in the art to use the sequence in the diagnostic method.

The Examiner is reminded that all questions of enablement should be evaluated against the claimed subject matter and the focus of the examination inquiry should be a question of whether everything within the scope of the claims is enabled (see MPEP 2164.08).

Accordingly, an Applicant is not required to enable material

which is not claimed. The pending claims do not recite any disease state other than Type II diabetes, nor do the pending claims recite identification of therapeutic avenues or methods of regulating the sequence or a disease state. Thus, no teachings regarding these issues are necessary in order to provide evidence for enablement of the pending claims.

The Examiner asserts that Applicants have not set forth any supporting evidence that suggests that any of the sequences (SEQ ID NOS:1 and 2) are unique molecular markers for Alzheimer's disease or any other disease and the prior art teaches that disease markers are highly unpredictable and require extensive experimentation.

The guidelines for a "test of enablement" indicate that if a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 USC 112, is satisfied (see MPEP 2164.01(c)).

Additionally, it has been established that the mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it (see MPEP 2164.02).

Applicants assert that SEQ ID NOS:1 and 2 are linked to Type II diabetes, however, do not claim that SEQ ID NOS:1 and 2 are unique markers for any particular disease or condition.

Although the prior art does not specifically recognize that the claimed markers are related to Type II diabetes, it does recognize that when a marker appears to be differentially expressed between a disease-state and a non-disease state, the marker is immediately recognized as a potential diagnostic marker, even if the involvement of the marker in the disease pathology is unknown. One of skill in the art would be familiar with this practice since it has been known in the art since at least 1992. See attached abstract of Gunnersen et al. (Proceedings of the National Academy of Science USA 89(24):11949-11953 1992; reference 3) in which the detection of glutamine synthetase in the cerebrospinal fluid of Alzheimer's disease patients lead to the suggestion of glutamine synthetase as a potential diagnostic biochemical marker for Alzheimer's disease. When one of skill in the art observes differential expression of the claimed peptides between patient having Type II diabetes and non-diseased patients; one of skill in the art would connect this peptide with potential diagnostics and/or therapeutics for Type II diabetes.

Thus, Applicants respectfully submit that since the specification demonstrates a link between the claimed markers (SEQ ID NOS:1 and 2) and Type II diabetes and that this link connotes the use the claimed markers in potential diagnostics and/or therapeutics of Type II diabetes, the requirement of "how to use" under 35 USC 112, first paragraph is satisfied.

Furthermore, Applicants respectfully submit that one of ordinary skill in the art would find the suggestion of a link between the claimed markers (SEQ ID NOS:1 and 2) and Type II diabetes to be reasonable.

It is known that ABC transporters are transmembrane proteins that function to transport molecules across cellular membranes utilizing energy derived from the hydrolysis of ATP (see attached articles; Dean et al. Genome Research 11:1156-1166 2001; reference 4 and Liu et al. Proceedings of the National Academy of Science USA 95(7):3495-3500 1998; reference 5). ABC transporters are involved in export of insulin from pancreatic β islet cells and thus contribute to the development of insulin deficiency and diabetes (see, for example, the attached article of Huopio et al. The Journal of Clinical Investigation 106(7):897-906 2000; reference 6). Huopio et al. disclose a mutation in the *SUR1* gene (an ABC transporter) that causes congenital hyperinsulinism in early life and predisposes to later insulin deficiency. Huopio et al. suspect that this mutation can be a cause of adult-onset diabetes (Type II).

At page 46, lines 4-10 of the specification as originally filed, the claimed marker (SEQ ID NO:1) is identified as an ABC transporter protein. SEQ ID NO:1 was isolated from serum samples obtained from normal patients but was not found in serum samples obtained from Type II diabetes patients. The instant inventors have

hypothesized that the function of this ABC transporter is absent and/or defective in Type II diabetes. One of skill in the art, having knowledge of the involvement of ABC transporters with diabetes, would find such a hypothesis to be reasonable.

Therefore, one of ordinary skill in the art would recognize the link between SEQ ID NO:1 and Type II diabetes and thus would also find the suggestion of SEQ ID NO:1 as marker for Type II diabetes entirely reasonable.

The Examiner asserts that the disclosure has not addressed issues taught in the prior art as crucial to the discovery of a biopolymer marker.

The Examiner cites an article Hampel *et al* (Journal of Neural Transmission 111:247-272 2004) which is allegedly relevant to the instant invention. According to the Examiner, Hampel *et al* reports on the difficulty involved in the discovery of marker candidates for Alzheimer's. The Examiner states that several required criteria must be met when determining a marker for Alzheimer's, including; indication of disease progression, heterogeneity of the clinical population, feasibility of testing, assay sensitivity, frequency of assessments, stability, standardization, dynamic range and comparative analysis. The Examiner seems to believe that since the specification allegedly lacks any of the criteria stated in the Hampel *et al* reference, it would require undue experimentation for one skilled in the art to make and use the invention.

Applicants respectfully assert that the criteria suggested by Hampel *et al* do not control the issue of enablement with regard to the instant invention. The guidelines for a "test of enablement" indicate that if a statement of utility in the specification contains within it a connotation of how to use, 35 USC 112 is satisfied. Applicants claim that the presence of a biopolymer marker selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:2 is linked to Type II diabetes; a statement which is enabled by the data presented in Figures 1-3. The claimed method involves a simple observation of the presence of the marker (as shown in Figure 1) in a gel, and conducting mass spectrometry analysis to identify the markers present in the gel. Hampel et al. disclose a study similar to that of the instant inventors; see page 260, last paragraph. In this study the content of body fluid obtained from MCI (mild cognitive impairment) patients was compared with the content of body fluid obtained from normal control patients. The MCI patients showed an elevated level of a protein, p-tau_{231}, in comparison to the healthy control patients. Hampel et al. deemed the results of this study adequate to suggest that high levels of p-tau_{231} may be a predictor for progressive cognitive decline in subjects with MCI. This disclosure of Hampel et al. demonstrates further that when elevated levels of proteins are found associated with a disease state, the protein is considered useful for potential diagnostics and/or therapeutics in the disease condition.

Thus, in contrast to the Examiner's assertion, the article of Hampel et al. lends support to the argument that the instant invention is enabled. Based upon the above-discussion, Applicants respectfully submit that compliance with the "required" criteria for a diagnostic assay according to Hampel *et al* is not necessary to show that the instant invention is enabled. When subjected to the "test for enablement" the Examiner's argument is not sufficient to support the enablement rejection; since the association of the claimed biopolymer markers (SEQ ID NOS:1 and 2) with Type II diabetes carries with it a connotation of use for diagnostics.

Similarly, the Examiner cites another article, Tockman *et al* (Cancer Research Supplement 52:2711s-2718s 1992) which is deemed to teach conditions necessary for a suspected cancer biomarker (intermediate end point marker) to have efficacy and success in a clinical application. The reference is drawn to biomarkers for early lung cancer detection, however the basic principles are applicable to other oncogenic disorders, according to the Examiner. Tockman *et al* is deemed to teach that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials. Early stage markers of carcinogenesis have clear biological plausiblity as markers of pre-clinical cancer if validated to a known cancer

outcome. Tockman *et al* is deemed to teach that the essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical disease and link those marker results with histological confirmation of disease.

Applicants respectfully disagree with the Examiner's reliance on the article by Tockman et al.

The Tockman *et al* article is concerned with early detection of lung cancer biomarkers and apparently does not discuss biomarkers for Type II diabetes.

Tockman et al. link several biopolymer markers to lung cancer in a manner analogous to that of the instant specification. Tockman et al. state at page 2712s, left column:

"A functional membrane-associated bombesin receptor recently has been isolated from human small cell lung carcinoma (NCI-H345) cells (23), and bombesin-like peptides have been found in the bronchial lavage fluid of asymptomatic cigarette smokers (24). Thus markers of growth factor expression, insofar as they reflect oncogene activation, may also hold promise for the detection of early (preneoplastic) lung cancer."

From this statement, it is clearly evident that Tockman et al. link bombesin with small cell lung cancer and associate it with potential diagnostics for small cell lung cancer. It does not appear that bombesin was "validated" and/or subjected to any

"criteria" prior to this association.

Additionally, Tockman et al. state at page 2713s, left column:

"Evidence of a transformed genome, by expression of tumor-associated antigens, oncofetal growth factors, or specific chromosomal deletions has clear biological plausibility as a marker of preclinical lung cancer."

From this statement, it appears that Tockman et al. believe that the expression of certain proteins provides evidence of a transformed genome and since this transformed genome is associated with lung cancer, it is reasonable to believe that these certain proteins are potential markers.

Such parallel reasoning between Tockman et al. and the instant specification, further supports Applicants contention that one of ordinary skill in the art would not have any difficulty seeing a link between the claimed biopolymer markers(SEQ ID NOS:1 and 2) and Type II diabetes.

Thus, Applicants respectfully submit that compliance with the "criteria" of Tockman et al. is not necessary in order to show that the instant invention is enabled.

Furthermore, it is noted that in chemical and biotechnical applications, evidence actually submitted to the FDA to obtain approval for clinical trials may be submitted to support enablement of an invention. However, considerations made by the FDA for approving clinical trials are different from those made by the PTO

in determining whether a claim is enabled (see *Scott v. Finney* 32 USPQ 2d 1115 and MPEP 2164.05).

The Examiner is reminded that the considerations made by the PTO involving clinical trials are less stringent than the considerations made by the FDA. Evidence presented by applicant to provide enablement of an invention need only be convincing to one of skill in the art and not conclusive.

Thus, Applicants respectfully submit that the instant specification is sufficient to convince one of ordinary skill in the art that the claimed biopolymer markers are linked to Type II diabetes; a contention which is supported by all of the above arguments.

In conclusion, Applicants claim that the differential expression of SEQ ID NO:1 and SEQ ID NO:2 between Type II diabetes patients and normal (with regard to Type II diabetes)control patients evidences a link between the claimed markers (SEQ ID NOS:1 and 2) and Type II diabetes; a statement which is enabled by the instant specification, as evidenced by the arguments presented herein. Applicants assert that one of ordinary skill in the art when reviewing the instant specification, given the level of knowledge and skill in the art, would recognize the link between the claimed biopolymer markers (SEQ ID NOS:1 and 2) and Type II diabetes and would further recognize how to use the claimed peptides (SEQ ID NOS:1 and 2) as markers for Type II diabetes.

Thus, Applicants respectfully request that this rejection under 35 USC 112, first paragraph now be withdrawn.

Rejections under 35 USC 102

Claims 1 and 2, as amended on April 2, 2002, stand rejected under 35 USC 102(b) as allegedly being anticipated by Wilson et al. (Science 282:2012-2018 1998).

The Examiner states that Wilson discloses sequences comprising or having SEQ ID NO:2. See GenCore protein search dated 8/3/04. Although the reference is silent with respect to the marker indicating a particular disease state like Alzheimer's disease, this is deemed inherent to the biopolymer. In other words, the sequences set forth in the claim would inherently be markers for the claimed diseases. Applicants SEQ ID NO:2 is disclosed as sequence identification number 5 (Q9N3X8) in the reference to Wilson. The Examiner alleges that therein the claimed sequence is taught.

Applicants note that neither the protein search the Examiner refers to (GenCore protein search dated 8/3/04) nor a copy of the Wilson reference was attached to the Office Action mailed on December 7, 2004. Applicants respectfully request that these documents be included within the Examiner's next communication to the Applicants.

Claim 1 has been amended to recite an isolated biopolymer

marker selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:2. Claim 2 has been cancelled. The term "analyte" has been removed from the claim.

The disclosure of Wilson et al. encompasses the entire genomic sequence of the nematode *Caenorhabditis elegans*. The claimed biopolymer marker SEQ ID NO:2 is a part of this entire sequence.

Claim 1, as instantly presented, recites specific markers (SEQ ID NOS:1 and 2). Furthermore, since "consisting of" is closed language and excludes any element, step or ingredient not specified in the claim (see MPEP 2111.03), the scope of the instant claim now encompasses only these two specific peptides (SEQ ID NOS:1 and 2) thus excluding the disclosure of Wilson et al. No where does Wilson et al. specifically teach the claimed biopolymer marker sequence (SEQ ID NO:2). Nor does Wilson et al. teach any peptide which is indicative of a link to Type II diabetes.

Accordingly, Applicants respectfully submit that the claim, as instantly presented, now distinguishes over the sequences taught by Wilson et al. and respectfully request that this rejection under 35 USC 102(b) be withdrawn.

Claims 1 and 2, as amended on April 2, 2002, stand rejected under 35 USC 102(a) as allegedly being anticipated by Finan et al. (Proceedings of the National Academy of Science USA 98(17):9889-9894 2001).

The Examiner states that Finan et al. disclose sequences comprising or having SEQ ID NO:1. See GenCore protein search dated 8/3/04. Although the reference is silent with respect to the marker indicating a particular disease state like Alzheimer's disease, this is deemed inherent to the biopolymer. In other words, the sequences set forth in the claim would inherently be markers for the claimed diseases. Applicants SEQ ID NO:1 is disclosed as sequence identification number 2 (C95985) in the reference to Finan et al. The Examiner alleges that therein the claimed sequence is taught.

Applicants note that neither the protein search the Examiner refers to (GenCore protein search dated 8/3/04) nor a copy of the Finan et al. reference was attached to the Office Action mailed on December 7, 2004. Applicants respectfully request that these documents be included within the Examiner's next communication to the Applicants.

Claim 1 has been amended to recite an isolated biopolymer marker selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:2. Claim 2 has been cancelled. The term "analyte" has been removed from the claim.

The disclosure of Finan et al. encompasses the entire genomic sequence of the 1,683-kb pSymB megaplasmid of *Sinorhizobium meliloti*. The claimed biopolymer marker SEQ ID NO:1 is a part of this entire sequence.

Claim 1, as instantly presented, recites specific markers (SEQ ID NOS:1 and 2). Furthermore, since "consisting of" is closed language and excludes any element, step or ingredient not specified in the claim (see MPEP 2111.03), the scope of the instant claim now encompasses only these two specific peptides(SEQ ID NOS:1 and 2) thus excluding the disclosure of Finan et al. No where does Finan et al. specifically teach the claimed biopolymer marker sequence (SEQ ID NO:1). Nor does Finan et al. teach any peptide which is indicative of a link to Type II diabetes.

Accordingly, Applicants respectfully submit that the claim, as instantly presented, now distinguishes over the sequences taught by Finan et al. and respectfully request that this rejection under 35 USC 102(a) be withdrawn.

Claims 1 and 2, as amended on April 2, 2002 stand rejected under 35 USC 102(a) as allegedly being anticipated by Galibert et al. (Science 293(5530):668-672 2001).

The Examiner states that Galibert et al. disclose sequences comprising or having SEQ ID NO:1. See GenCore protein search dated 8/3/04. Although the reference is silent with respect to the marker

indicating a particular disease state like Alzheimer's disease, this is deemed inherent to the biopolymer. In other words, the sequences set forth in the claim would inherently be markers for the claimed diseases. Applicants SEQ ID NO:1 is disclosed as sequence identification number 2 (C95985) in the reference to Galibert et al. The Examiner alleges that therein the claimed sequence is taught.

Applicants note that neither the protein search the Examiner refers to (GenCore protein search dated 8/3/04) nor a copy of the Galibert et al. reference was attached to the Office Action mailed on December 7, 2004. Applicants respectfully request that these documents be included within the Examiner's next communication to the Applicants.

Claim 1 has been amended to recite an isolated biopolymer marker selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:2. Claim 2 has been cancelled. The term "analyte" has been removed from the claim.

The disclosure of Galibert et al. encompasses the composite genome of *Sinorhizobium meliloti*. The claimed biopolymer marker SEQ ID NO:1 is a part of this genome.

Claim 1, as instantly presented, recites specific markers (SEQ ID NOS:1 and 2). Furthermore, since "consisting of" is closed language and excludes any element, step or ingredient not specified in the claim (see MPEP 2111.03), the scope of the instant claim now

encompasses only these two specific peptides(SEQ ID NOS:1 and 2) thus excluding the disclosure of Galibert et al. No where does Galibert et al. specifically teach the claimed biopolymer marker sequence (SEQ ID NO:1). Nor does Galibert et al. teach any peptide which is indicative of a link to Type II diabetes.

Accordingly, Applicants respectfully submit that the claim, as instantly presented, now distinguishes over the sequences taught by Galibert et al. and respectfully request that this rejection under 35 USC 102(a) be withdrawn.

CONCLUSION

In light of the foregoing remarks, amendments to the specification and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,

Ferris H. Lander
Registration # 43,377

McHale & Slavin, P.A.
2855 PGA Boulevard
Palm Beach Gardens, FL 33410
(561) 625-6575 (Voice)
(561) 625-6572 (Fax)
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